Should single- or two-stage revision surgery be used for the management of an infected total knee replacement? A critical review of the literature

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Abstract
Introduction
A post-operative periprosthetic infection of total knee replacement (TKR) is one of the most devastating complications for a patient to endure after surgery and is a challenge for the orthopaedic surgeon to treat. In this paper, we present the current evidence to support a single-stage revision of a TKR for periprosthetic infection and compare the outcome with that of a two-stage revision procedure. In addition, we also outline the methods of diagnosis used to identify a periprosthetic infection of a TKR.

Conclusion
The current evidence-based surgical options to manage periprosthetic infection do not offer a 100% guarantee of eradication of the infection. As to whether a single- or a two-stage procedure should be undertaken needs to be personalized to each patient and their circumstances.

Introduction
A post-operative periprosthetic infection (PPJI) of total knee replacement (TKR) is one of the most devastating complications for a patient to endure after surgery and is a challenge for the orthopaedic surgeon to treat. The rate of periprosthetic infection of TKR varies and is dependent upon the length of follow-up, but it is generally accepted that the rate is between 0.4% and 2%1. This rate is however increased for patients who have specific comorbidities and for those undergoing revision surgeries2. Potentially, such an infection can lead to loss of limb or life, and will likely require revision surgery. The type and extent of the revision surgery are diverse and dependent upon the patient’s circumstances and time of presentation from initial surgery3. Multiple management options are open to the orthopaedic surgeon treating such infection, but some are accepted while others remain controversial. In this paper, we present the evidence to support a single (one)-stage revision for periprosthetic infection of a TKR; however, this intervention is only indicated for specific case scenarios, and a knowledge of the diagnosis and classification of such an infection is essential and will be discussed first.

Pathology and microbiology
The majority, approximately half, of microorganisms infecting knee prostheses are the different strains of Staphylococci, with coagulase-negative Staphylococci being the most common, accounting for approximately 27% of infections and Staphylococcus aureus being second and responsible for 23% of infections. The microorganism attaches itself to the surface of the prosthesis and produces a biofilm, which forms between 36 h and 3 weeks. There are four consecutive steps in biofilm formation: adherence to the surface of prosthesis, production of the biofilm, maturation of the biofilm, and finally its detachment and spread of the microorganisms, which then result in overwhelming infection of the prosthesis clinically. The biofilm blocks the body’s natural immune defence mechanisms, and the microorganisms exist in a planktonic form within their protected environment. The biofilm contains polysaccharide molecules, proteins and extracellular DNA, and replicate slowly; these are termed sessile bacteria. The ability of the pathogen to produce a biofilm defines its virulence in prosthetic infection, being resistant to antibiotics with a minimal inhibitory concentration that can be elevated up to 1000 times with the biofilm5. Commensal bacteria, such as coagulase-negative Staphylococci are more frequent in immediate and early prosthetic infections, when spread from the surgical wound edges and in late low-grade infections. In late infections by haematogenous spread, Staphylococcus aureus is the most important causative factor6. The clinical signs and symptoms

Diagnosis
The key to effectively managing patients with a prosthetic infection of a TKR is early and accurate diagnosis. The presentation can, however, be varied and a definitive diagnosis may be challenging. There is no definitive single test to establish a diagnosis, and relies on a combination of clinical signs and symptoms, laboratory investigations and radiographic studies.

Clinical signs and symptoms
There is a vast spectrum of clinical presentations of patients suffering with a prosthetic joint infection7, which can vary from systemic sepsis to chronic indolent low-grade infection. The patient may complain
of pain, swelling, chronic soft tissue induration/oedema, erythema, warmth, with limitation or worsening knee function and may have a discharging wound or draining sinus (Figure 1); however, most patients may only have a few of these symptoms and signs.

Laboratory tests

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) offer excellent diagnostic information for establishing the presence or absence of prosthetic joint infection. Greidanus et al. identified that an ESR of >22.5 mm/h and a CRP of >13.5 mg/l offered a sensitivity rate of 0.93 and 0.91, and a specificity of 0.83 and 0.86, respectively. After index surgery, the CRP should return to normal within 3–6 weeks. Serum interleukin-6 is probably a more accurate diagnostic test, as it correlates positively with the presence of peri-prosthetic infection. Di Cesare et al. conducted a prospective case–control study of 58 patients undergoing revision surgery of total hip and knee replacements; serum Interleukin-6 values > 10 pg/ml were demonstrated to have a sensitivity of 100%, specificity of 95%, positive predictive value of 89%, negative predictive value of 100% and accuracy of 97%.

Knee aspirate cell and differential counts

In a patient with TKR who is suspected to have a prosthetic joint infection, an aspiration of the joint should be obtained. This does carry a risk of potentially infecting the TKR, if it is not already, and with such a risk this should be carried out under a strict aseptic technique in an operating theatre. Synovial fluid cell count and differential is a very useful diagnostic test. If the white cell count is greater than 1100/ml and the neutrophil percentage is 65% or more, the positive predictive value is 98.6%, whereas if both the values are below this, the negative predicted rate is 98.2%.

Antibiotics should be suspended, if possible, for 10–14 days before carrying out the aspiration, and should be cultured for at least 2 weeks as one in four cultures that are negative at 7 days will have positive growth by 14 days.

Polymerase chain reaction (PCR)

Molecular diagnosis using PCR to amplify strains of bacterial DNA enables identification of the potential pathogen. It can be used to identify non-viable bacteria and is thought to be a quick method, and whether a patient has received antibiotics does not affect this method. However, a high percentage of false-negative test results have been reported using such methodology.

Ultrasonication

The biofilm formed over the surface of the implant by the microorganism can prevent growth and identification of the pathogen. Ultrasonication lyses the bacteria, making them void to culture, and then PCR can be used to identify the pathogen. Trampuz et al. demonstrated that cultures of samples obtained by the process from the prostheses were more sensitive than tissue cultures for the microbiologic diagnosis of prosthetic joint infection, especially in patients...
who had received antibiotics within 14 days of surgery.

Intra-operative frozen section and gram staining
Frozen histological sections are used to assist decision-making in cases with equivocal serum inflammatory makers and aspirate cytology. The cut-off value of more than five neutrophils per high-power field at a magnification of 400× is commonly used for the diagnosis of infection. The sensitivity and specificity are both more than 80%\(^\text{15}\). Intra-operative gram staining is an unreliable test, with a sensitivity of 27%\(^\text{16}\), and should not be used routinely.

Plain radiographs
Potential signs of loosening with rapidly progressive radiolucent lines surrounding an implant may be present during an infection, which can progress with resorption of subchondral bone and patchy osteoporosis and eventual osteolysis (Figure 2).

Nuclear imaging
A bone scan using technetium 99 can help confirm a diagnosis, but the cost is relatively high; although the level of sensitivity is high and level of specificity remained low, its use is restricted\(^\text{17}\). A technetium bone scan remains positive more than 1 year after implantation because of increased periprosthetic bone remodelling. Overall, the potential value of

| Table 1. Relative contraindications to attempt single-stage revision surgery for a periprosthetic infection suggested by Oussedik et al. |
|---------------------------------|---------------------------------------------------------------|
| Category                        | Compromising factor                                            |
| Local                           | Significant soft tissue compromise                              |
|                                 | Significant bone loss precluding cemented fixation             |
| Host                            | Immunosuppression                                              |
|                                 | Concurrent sepsis                                              |
|                                 | Systemic disease                                               |
|                                 | Re-infection                                                  |
| Organism                        | Multi-resistant organism (MRSA)\(^a\)                         |
|                                 | Polymicrobial infection                                        |
|                                 | Unusual commensals                                             |
|                                 | Unusual resistance profiles                                    |
|                                 | Unidentified infective organism                                 |

\(^a\)Methicillin-resistant Staphylococcus aureus

**Figure 3:** The wound before (a) and after (b) through debridement and lavage of the soft tissues and bone ends of a chronically infected TKR.
Table 2. Published studies reporting the outcome of the patients undergoing single-stage revision for a periprosthetic infection of their TKR

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Follow-up</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Foerster et al.</td>
<td>1991</td>
<td>118</td>
<td>5–15</td>
<td>64</td>
</tr>
<tr>
<td>Goksan and Freeman</td>
<td>1992</td>
<td>18</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>Lu et al.</td>
<td>1997</td>
<td>8</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Siegel et al.</td>
<td>2000</td>
<td>31</td>
<td>2–15</td>
<td>71</td>
</tr>
<tr>
<td>Buechel</td>
<td>2004</td>
<td>22</td>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>Soudry et al.</td>
<td>2009</td>
<td>20</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>Parkinson et al.</td>
<td>2011</td>
<td>12</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>229</td>
<td></td>
<td>86</td>
</tr>
</tbody>
</table>

Table 2. Published studies reporting the outcome of the patients undergoing two-stage revision for a periprosthetic infection of their TKR

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Follow-up</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insall et al.</td>
<td>1983</td>
<td>11</td>
<td>2.8</td>
<td>100</td>
</tr>
<tr>
<td>Hansen et al.</td>
<td>1994</td>
<td>89</td>
<td>4.3</td>
<td>89</td>
</tr>
<tr>
<td>Goldman et al.</td>
<td>1996</td>
<td>64</td>
<td>7.5</td>
<td>91</td>
</tr>
<tr>
<td>Gaccon et al.</td>
<td>1997</td>
<td>29</td>
<td>3.5</td>
<td>83</td>
</tr>
<tr>
<td>Hirakawa et al.</td>
<td>1998</td>
<td>55</td>
<td>5.2</td>
<td>87</td>
</tr>
<tr>
<td>Haddad et al.</td>
<td>2000</td>
<td>45</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>Siebel et al.</td>
<td>2002</td>
<td>10</td>
<td>1.1</td>
<td>100</td>
</tr>
<tr>
<td>Pietsch et al.</td>
<td>2003</td>
<td>24</td>
<td>1.2</td>
<td>96</td>
</tr>
<tr>
<td>Haleem et al.</td>
<td>2004</td>
<td>96</td>
<td>7.2</td>
<td>91</td>
</tr>
<tr>
<td>Soudry et al.</td>
<td>2009</td>
<td>21</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>444</td>
<td></td>
<td>93</td>
</tr>
</tbody>
</table>

Bone scanning for the diagnosis of PPJI remains controversial.

Classification
Multiple classifications for infected total joint replacement exist; however, that described by Tsukayama et al.\(^5\) seems to be accepted by most authors. They defined four groups based upon the clinical presentation of the patient that also aids management decisions. Group one is when there are positive intra-operative cultures (two or more) obtained during the revision procedure, when no infection was suspected pre-operatively. Group two infections are those that occur in the early post-operative period, within 1 month of the index procedure. Group three is a haematogenous infection, where the TKR performed well prior to the acute episode, due to seeding of the implant from a distant source. Group four includes those patients with chronic infections of their TKR that are persistent beyond 1 month after index procedure. Although not used universally, classification systems, also taking into account the host situation, are considered to be of better prognostic value\(^6\).

Surgical management
The management of the infected TKR is complex and expensive, with an ultimate goal of eradicating the infection and leaving the patient with a pain-free and functioning TKR. The treatment options include: debridement and irrigation (+/- polyethylene exchange), single- or two-stage revision, resection arthroplasty and more rarely arthrodesis or amputation, or long-term antibiotic suppression\(^7\). Debridement and irrigation (+/- polyethylene exchange) may be used for group 2 periprosthetic infections, but the success rate of this is poor, with an eradication rate of 18%–39%\(^1\). Group 3 and 4 infections can be managed with revision of the prosthesis, which may be a single- or a two-staged procedure\(^3\). Insall et al.\(^21\) first described a two-stage procedure in 1983 for chronic indolent periprosthetic infections of TKRs. The first stage of this procedure is radical debridement through the original incision, with removal of the component, all cement, membranes, and infected tissue (Figure 3). Antibiotics are withheld until multiple (at least 5) deep tissue specimens have been obtained using new instruments each time to ensure no cross contamination. A thorough lavage of the wound is then undertaken. A static (non-articulating Figure 4]) or a dynamic (articulating) spacer, which is antibiotic laden, is then used to bridge the deficit. This is the end of the first stage, and the patient is placed on antibiotics for 6–8 weeks (depending on sensitivities from the intra-operative specimens). The patient’s clinical status and inflammatory markers are observed for this period and after cessation of the antibiotics, only when the infection is thought to be eradicated is the second stage undertaken, which maybe 6 weeks to 6 months after the first stage. The second stage then entails...
re-implantation of the TKR, which may need to be a modular semi-constrain (Figure 5) or hinged prosthesis due to bone and soft tissue loss. A success rate of 85% at 10 years was reported for this method of revision TKR for periprosthetic infections. However, this two-staged procedure results in two hospital admissions, morbidity associated with the second procedure, poor mobility and pain between the stages endured by the patient, in addition to the financial implications for both the healthcare service and the patient. A single-stage revision for periprosthetic infection of a TKR is a potential alternative that averts the second admission with immediate benefit to the patient, and offers financial savings.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies were conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies were approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Single-stage revision

A single-stage revision is advocated by some orthopaedic surgeons in specific case scenarios. Oussedik et al. proposed a list of potential contraindications to a single-stage revision surgery (Table 1), however, this was based on periprosthetic infections of total hip replacements. One important criterion that is generally accepted is that the organism causing the infection must be identified pre-operatively and has known antibiotic sensitivities, which enables the correct intravenous antibiotics and antibiotic loaded cement to be used at the time of surgery. Identical to the first part of the two-stage revision of all foreign material, synovium, prosthesis and cement are removed with through lavage of the remaining tissue. At this point, the wound is packed with 'new' sterile swabs and the wound is bandaged with release of the tourniquet. There is a short break, this gives the staff and surgeon time to change all instruments and re-scrub for the next part of the case. The tourniquet is re-inflated and the patient is re-draped and the second part of the single-stage revision commences with re-implantation of the revision prosthesis. Antibiotics should continue throughout the perioperative period and are prescribed according to sensitivities. Immediate rehabilitation should be commenced, with full weight bearing and range of movement exercises once the wound is considered dry.
Outcome of single- versus two-stage revision

The success rate of single-stage revision for periprosthetic infection of TKR is variable and seems dependent upon the length of follow-up (Table 2, Figure 6), from 100% at 2 years\textsuperscript{23,26} to 64% at 10 years\textsuperscript{24}. According to seven published studies, we identified from the literature the overall average survival rate was 86% 6 years from the index procedure (Table 2)\textsuperscript{23,24,26–30}. This pooled survival rate is not as good as that offered by two-stage revision surgery, where the overall pooled average survival for those studies reporting the outcome of such surgery is 93% at a mean of 4.5 years follow-up (Table 3)\textsuperscript{21,22,30–37}. Upon pooling the data from Tables 2 and 3, there were 32 failures in the 7 studies reporting the survival after single-stage surgery and 31 for those studies reporting the survival after two-stage surgery. This data suggests that the risk of failure to eradicate the infection is significantly greater when employing a single-stage strategy for infection (odds ratio 2.16, 95% confidence interval 1.28–3.64, \(p = 0.003\)). However, there is only one study comparing the eradication rate between single- and two-stage procedures, which demonstrated no differences between these procedures\textsuperscript{38}. In addition, they did show that the single-stage had a better functional outcome. Hence, it would seem that two-stage re-implantation is the gold standard for eradication of infection in management of peri-
prosthetic TKR infections. However, single-stage revision is appealing for specific case scenarios that averts an additional surgical procedure and the associated patient morbidity, and may result in a better functional outcome.

Conclusion

Periprosthetic infection after TKR continues to be a devastating complication that has to be endured by our patients, and although the prevalence is <2% with the increasing rate of TKR, there will be more and more patients presenting to orthopaedic services with an infected TKR. The current evidence-based surgical options to manage periprosthetic infection do not offer a 100% guarantee of eradication of the infection. As to whether a single- or a two-stage procedure should be undertaken needs to be personalized to each patient and their circumstances. Currently, evidence would suggest that two-stage revision is the gold standard and offers more than a 90% chance of eradication of the infection. However, such an undertaking results in two separate interventions that carry peri-operative morbidity and a period of disability for patients between their two stages. In contrast, a single-stage procedure, in the right patient, offers a definitive intervention with immediate benefit and commencement of rehabilitation. Furthermore, from what little evidence exists, the functional outcome would seem to be better with the single-stage procedure, but this may be influenced by multiple case-mix factors. It would seem that both single- and two-stage revision procedures for infection of TKR offer advantages and disadvantages to our patients. Hence, patients who would be applicable for a single-stage revision should be made aware of these risks and benefits of both options, and should be engaged in the decision as to whether a single- or a two-stage revision should be undertaken. Despite the presented evidence for both procedures they only offer partial success in eradication of infection and new modalities should be investigated.

References


